Exhibit 16

NIH NATIONAL CANCER INSTITUTE

Ovarian, Fallopian Tube, and Primary Peritoneal Cancers Prevention (PDQ®)–Health Professional Version

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Who Is at Risk?

Ovarian cancer is a rare disease, with carcinomas comprising approximately 90% of tumors and germ cell and stromal tumors accounting for the remainder. Ovarian carcinoma is a disease that predominantly affects postmenopausal women. Ovarian carcinomas consist of several histopathological types, with high-grade serous being both the most common and most lethal. The category of ovarian borderline tumor or tumor of low-malignant potential, which historically had been considered in the context of ovarian cancer, is now generally considered a nonmalignant entity, although it has a postulated relationship with the development of some histological subtypes of low-grade ovarian carcinomas.[1]

Risk factors for ovarian cancer include a family history of breast and/or ovarian cancer and inheritance of deleterious mutations in *BRCA1*, *BRCA2*, and selected other high-penetrance genes.[2-6] For more information, see Genetics of Breast and Gynecologic Cancers. Other risk factors for ovarian cancer include obesity, tall height, endometriosis, and the use of postmenopausal hormone therapy.[7-9]

Associations of some risk factors with ovarian cancer vary by histopathological subtype. The association of endometriosis with ovarian cancer is stronger for nonserous subtypes, especially clear cell carcinoma and endometrioid subtypes.[10] Further, among carriers of deleterious mutations in *BRCA1* or *BRCA2*, increasing evidence suggests that many tumors previously classified as ovarian high-grade serous carcinoma may develop from malignant cells arising in the tubal epithelium (serous tubal intraepithelial carcinoma [STIC]), although these tumors continue to be referred to as *ovarian* cancers in most writings. It is hypothesized that high-grade serous carcinomas among individuals who are not carriers of mutations in *BRCA1* or *BRCA2* may also develop in the fallopian tube, but few STICs have been identified among these women in the absence of concurrent high-stage disease. Further, data suggest that the distinction of high-grade serous carcinomas from other histological types of high-grade carcinomas, particularly endometrioid carcinomas, is not reliable. Reported rates of mucinous carcinoma diagnoses have declined dramatically, but expert pathology reviews suggest that

this reflects increased recognition of metastases from occult gastrointestinal primary tumors to the ovary, rather than a true decline in rates of ovarian primary tumors.[11]

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Overview

Note: The Overview section summarizes the published evidence on this topic. The rest of the summary describes the evidence in more detail.

Other PDQ summaries on Ovarian, Fallopian Tube, and Primary Peritoneal Cancers Screening and Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment are also available.

Factors With Adequate Evidence of an Increased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

Family history and inherited susceptibility to ovarian, fallopian tube, and primary peritoneal cancers

Based on solid evidence, women with a family history of ovarian cancer, especially in a first-degree relative, and those with an inherited predisposition to ovarian cancer, such as a *BRCA1* or *BRCA2* mutation, have an increased risk of developing ovarian cancer. For more information, see Genetics of Breast and Gynecologic Cancers.

Endometriosis

Based on fair evidence, self-reported and laparoscopically confirmed endometriosis is associated with an increased risk of ovarian cancer.[1,2] The association is stronger with nonserous histological subtypes, specifically endometrioid and clear cell carcinomas.[2,3]

Magnitude of Effect: Modest with observed relative risks (RRs) of 1.8 to 2.4.

Study Design: Cohort and case-control studies.

Internal Validity: Good.

Consistency: Fair.

External Validity: Good.

Hormone replacement therapy

Based on fair evidence, current or recent hormone therapy is associated with a small increased risk of ovarian cancer. Risks attenuate after hormone therapy is discontinued. Risks did not differ by oral preparation type (estrogen only vs. combined estrogen/progestin).[4,5] Cutaneous hormone therapy may have a lower risk than oral hormone therapy.[6]

Magnitude of Effect: Modest with observed RRs of 1.20 to 1.8.

Study Design: One randomized clinical trial, cohort and case-control studies.

Internal Validity: Good.

Consistency: Fair.

External Validity: Good.

Obesity and height

Based on fair evidence, increases in height and body mass index (BMI) are associated with a modest increased risk of ovarian cancer.

Magnitude of Effect: Based on an overview analysis of 25,157 women with ovarian cancer and 81,211 women without ovarian cancer from 47 epidemiological studies, the RR of ovarian cancer per 5 cm increase in height is 1.07 (95% confidence interval [CI], 1.05–1.09). The RR of ovarian cancer per 5 kg/m^2 increase in BMI is 1.10 (95% CI, 1.07–1.13) among never-users of hormone therapy and 0.95 (95% CI, 0.92–0.99) among ever-users of hormone therapy.[7]

Study Design: Cohort and case-control studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Factors With Adequate Evidence of a Decreased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

Oral contraceptives: benefits

Based on solid evidence, oral contraceptive use is associated with a decreased risk of developing ovarian cancer.

Magnitude of Effect: The degree of risk reduction varies by duration of oral contraceptive use and time since last use. A prospective, contemporary, nationwide cohort study of women aged 15 to 49 years in Denmark found that any use of hormonal contraception was associated with an absolute reduction in the rate of ovarian cancer of 3.2 cases per 100,000 person-years. The reduction in risk persists for more than 30 years after use is discontinued, but the degree of reduction attenuates over time.[8]

Study Design: Multiple case-control and cohort studies; meta-analyses.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Oral contraceptives: harms

Based on solid evidence, combined current use of estrogen-progestin oral contraceptive use is associated with an increased risk of venous thromboembolism, particularly among smokers, for whom use is contraindicated. Oral contraceptives are not associated with a long-term increased risk of breast cancer but may be associated with a short-term increased risk while a woman is taking oral contraceptives. The risk of breast cancer declines with time since last use.

Magnitude of Effect: The risks may vary by preparation. Overall, the absolute risk of venous thromboembolism is about three events per 10,000 women per year while taking oral contraceptives. The risk is modified by smoking. Breast cancer risk among long-term (>10 years) current users is estimated at one extra case per year per 100,000 women. The risk dissipates with time since last use.

Study Design: Observational studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Tubal ligation: benefits

Based on solid evidence, tubal ligation is associated with a decreased risk of ovarian cancer.

Magnitude of Effect: Adjusting for other forms of contraception, tubal ligation provides a relative reduction in the odds of developing ovarian cancer of about 30%.

Study Design: Multiple case-control studies and cohort studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Tubal ligation: harms

Based on fair evidence, harms include surgical risks, including the following:[9]

- Major morbidity including blood transfusion, reoperation, or hospital readmission (rate of 1.0 per 100 procedures).
- Minor morbidity including postoperative fever, urinary tract infections, or wound infections (rate of 6.0 per 100 procedures).

Multiparity

Based on good evidence, multiparity is associated with a decreased risk of ovarian cancer.

Magnitude of Effect: Based on good evidence from multiple observational epidemiological studies, parous women have an approximately 30% lower ovarian cancer risk than nulliparous women.[7,10-12]

Study Design: Observational epidemiological studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Salpingectomy

Based on limited data, salpingectomy is associated with a decrease in risk of ovarian cancer.

Magnitude of Effect: Approximately 50% decrease for bilateral salpingectomy, less protection for unilateral salpingectomy.

Study Design: Observational epidemiological studies from several different countries.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Breastfeeding

Based on solid evidence, breastfeeding is associated with a decreased risk of ovarian cancer.

Magnitude of Effect: 2% decrease with every month of breastfeeding.[13]

Study Design: Multiple case-control and cohort studies; meta-analysis.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Risk-reducing bilateral salpingo-oophorectomy: benefits

Based on solid evidence, risk-reducing bilateral salpingo-oophorectomy is associated with a decreased risk of ovarian cancer. Peritoneal carcinomatosis has been reported rarely following surgery. Risk-reducing surgery is generally reserved for women at high risk of developing ovarian cancer, such as women who have an inherited susceptibility to ovarian cancer.

Magnitude of Effect: 90% reduction in risk of ovarian cancer observed among women with a *BRCA1* or *BRCA2* mutation.

Study Design: Multiple case-control studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Risk-reducing bilateral salpingo-oophorectomy: harms

Based on solid evidence, prophylactic oophorectomy among women who are still menstruating at the time of surgery is associated with infertility, vasomotor symptoms, decreased sexual interest, vaginal dryness, urinary frequency, decreased bone-mineral density, and increased cardiovascular disease.

Magnitude of Effect: Reported prevalence of vasomotor symptoms varies from 41% to 61.4% among women who underwent oophorectomy before natural menopause. Women with bilateral oophorectomy who did not take hormone therapy were twice as likely to have moderate or severe hot flashes, compared with women who underwent natural menopause. The RR of cardiovascular disease among women with bilateral oophorectomy and early menopause was 4.55 (95% CI, 2.56–9.01).

Study Design: Cohort and case-control studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Areas of Uncertainty

Ovarian hyperstimulation for infertility treatment

Evidence is poor to determine the association between ovarian hyperstimulation and the risk of ovarian cancer. Risk of ovarian cancer may be increased among women who remain nulligravid after being treated with ovarian stimulating medications.

Magnitude of Effect: Uncertain—risk of invasive ovarian cancer may be increased among women who remain nulligravid after treatment; risk of borderline ovarian tumors may be increased among women treated with infertility drugs.

Study Design: Cohort and case-control studies; systematic review.

Internal Validity: Fair.

Consistency: Poor.

External Validity: Fair.

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Incidence and Mortality

In 2024 in the United States, ovarian cancer will cause an estimated 19,680 new cases and 12,740 deaths.[1] Based on statistical models for analysis, rates for new ovarian cancer cases have been falling, on average, by 3.3% each year from 2010 to 2019. Death rates fell, on average, by 2.8% each year from 2011 to 2020.[2] In 2020, the overall incidence rate for ovarian carcinoma among women aged 65 years and older was 30.4 cases per 100,000 women-years.[3] Given that the Surveillance, Epidemiology, and End Results (SEER) Program does not adjust for oophorectomy or salpingectomy, racial differences in the prevalence of women who have undergone these procedures could bias racial rate comparisons. A statistically significant decrease in delayed adjusted incidence of 1.7% among White women from 2000 to 2015 and 0.6% among Black women from 2000 to 2016 was observed. A statistically significant decrease in mortality rates of 2.4% per year among White women from 2005 to 2017 and 1.8% per year among Black women from 2003 to 2020 was observed. The population lifetime risk of ovarian cancer is 1.15%; the population lifetime risk of dying from ovarian cancer is 0.77%.[3]

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Histology and Pathogenesis of Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

Ovarian carcinoma is a biologically and clinically heterogeneous class of tumors that includes several major subtypes: serous, mucinous, endometrioid, and clear cell. Classification of ovarian carcinomas into type I and type II tumors has been proposed. In this system, type I tumors include the following:[1]

1. Endometriosis-related subtypes, such as endometrioid, clear cell, and seromucinous.
2. Low-grade serous.
3. Mucinous and malignant Brenner tumors.

Among type I tumors, endometrioid and clear cell carcinomas are most common and most important clinically. In general, type I ovarian carcinomas present at a lower stage than type II tumors and portend a better prognosis.

Type II tumors are comprised mainly of high-grade serous carcinomas, the most common and lethal of all ovarian carcinoma subtypes. These cancers usually present with symptomatic bulky stage III or IV disease and ascites. Many, but possibly not all, high-grade serous carcinomas appear to arise from malignant *in situ* lesions in the epithelium of the fallopian tube fimbria. These lesions spread to the ovaries secondarily but continue to be referred to as ovarian carcinomas. Evidence for a tubal origin is based mainly on examination of risk-reducing salpingo-oophorectomy specimens, performed among *BRCA1/BRCA2* mutation carriers, in which incidental low-volume disease enables recognition of serous tubal intraepithelial carcinoma (STIC). However, not all women with high-grade serous carcinomas have identifiable STIC, and few studies of the fallopian tubes of women who are not carriers of *BRCA1/BRCA2* mutations have been performed, suggesting that pathogenesis of these tumors is not fully known. Serous carcinomas can be further divided on the basis of molecular characteristics.[2]

The heterogeneity in the etiology and pathogenesis of different ovarian cancer subtypes and variability in the classification of tumors over time and between studies pose challenges for interpretation of etiological data. Ovarian cancer is rare, thus sample size and power of studies to detect moderate associations by cancer subtype is limited. However, clearer subtyping of cancers may help improve our understanding of the etiology of ovarian malignancies in future studies.

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Factors With Adequate Evidence of an Increased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

Family History and Inherited Susceptibility to Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

Some women are at an increased risk of these cancers because of an inherited mutation, with the magnitude of that risk dependent on the affected gene and specific mutation. Underlying ovarian cancer risk can be assessed through accurate pedigrees and/or genetic markers of risk. Because of uncertainties about cancer risks associated with certain specific gene mutations, genetic information may be difficult to interpret outside of families with a high incidence of ovarian cancer.

This summary does not address multiple genetic syndromes or women who are at high risk because of inherited genetic factors. For specific information related to ovarian cancer risk associated with multiple genetic syndromes and ovarian cancer in *BRCA1/BRCA2* mutation carriers, see Genetics of Breast and Gynecologic Cancers and Genetics of Colorectal Cancer.

Endometriosis

Endometriosis has been associated with a modestly increased risk of ovarian cancer. The association is stronger with nonserous histological subtypes, specifically endometrioid and clear cell carcinomas. In one analysis, data were pooled from 13 ovarian cancer case-control studies, including 13,226 controls and 7,911 women with invasive ovarian cancer who were part of the Ovarian Cancer Association Consortium. Logistic regression analyses were undertaken to assess the association between self-reported endometriosis and risk of ovarian cancer. Self-reported endometriosis was associated with a significantly increased risk of clear cell (odds ratio [OR], 3.05; 95% confidence interval [CI], 2.43–3.84; $P < .0001$), low-grade serous (OR, 2.11; 95% CI, 1.39–3.20; $P < .0001$), and endometrioid invasive ovarian cancers (OR, 2.04; 95% CI, 1.67–2.48; $P < .0001$). No association was noted between endometriosis and risk of mucinous (OR, 1.02; 95% CI, 0.69–1.50; $P = .93$) or high-grade serous invasive ovarian cancer (OR, 1.13; 95% CI, 0.97–1.32; $P = .13$), or borderline tumors of either subtype (OR, 1.20; 95% CI, 0.95–1.52; $P = .12$ for serous and OR, 1.12; 95% CI, 0.84–1.48; $P = .45$ for mucinous).[1] Considering that the clear cell and endometrioid ovarian cancers represented approximately 15% of all ovarian cancers, the lifetime risk of these histological subtypes is approximately 0.2%, which, on the basis of these data, would increase to approximately 0.4% to 0.6% in the presence of self-reported endometriosis.

A cohort study from the Danish National Patient Register identified 45,790 women with a clinical diagnosis of endometriosis between 1977 and 2012. Data were linked to the Danish Cancer Register, which identified 186 women with a diagnosis of ovarian cancer. Endometriosis was associated with modestly increased risks of ovarian cancer overall (standardized incidence ratio [SIR], 1.34; 95% CI, 1.16–1.55). This was primarily caused by increases in endometrioid (SIR, 1.64; 95% CI, 1.09–2.37) and clear cell subtypes (SIR, 3.64; 95% CI, 2.36–5.38). No increased risk of serous or mucinous histological subtypes was reported.[2]

Using data from the Nurses' Health Study II, 228 ovarian cancers were identified from among 102,025 eligible women. Cox proportional hazards regression models were used to assess associations between endometriosis and cancer risk, evaluating the impacts of self-reported versus laparoscopically confirmed endometriosis, delayed diagnosis, and postendometriosis diagnosis changes in risk-factor exposures. Self-reported endometriosis was associated with ovarian cancer (relative risk [RR], 1.81; 95% CI, 1.26–2.58), which was stronger for laparoscopically confirmed endometriosis diagnoses (RR, 2.14; 95% CI, 1.45–3.15). Diagnosis delays or postendometriosis diagnosis changes in risk factors had little impact on risk. Although this study had limited power to detect differences in risk on the basis of histological subtype, nonserous cases were shown to have an increased risk (RR, 2.44; 95% CI, 1.48–4.01), and serous cases were not (RR, 1.69; 95% CI, 0.92–3.11).[3] A large case-control study in African American women found similar associations with a history of endometriosis and ovarian cancer (OR, 1.78; 95% CI, 1.09–2.90), suggesting that findings from populations of predominantly White women are also observed in Black women.[4]

Hormone Replacement Therapy/Hormone Therapy

A meta-analysis of 52 studies (17 prospective and 35 retrospective) including 21,488 ovarian cancers found increased risks with current or recent hormone replacement use in prospective studies (RR, 1.37; 95% CI, 1.29–1.46), with similar results for retrospective designs. Significant relationships were found for serous and endometrioid subtypes.[5] Recent use was strongly related to risk even among women who had used hormone replacement therapy for less than 5 years (RR, 1.41; 95% CI, 1.32–1.50). Risk declined among women who had discontinued use, with greater effects for longer periods of cessation. Risks did not differ by preparation types (estrogen only vs. combined estrogen/progestin). Risks also did not differ by age at use.[6,7] Cutaneous hormone therapy may have a lower risk than oral hormone therapy.[8]

Tibolone, a synthetic steroid with estrogenic, progestogenic, and androgenic properties, has been associated with an increased incidence rate ratio of 3.56 (95% CI, 3.08–4.69) for endometrial cancer for current users compared with never-users. Tibolone is approved for use to manage menopausal symptoms or to prevent osteoporosis in many countries. However, it is not approved for use in Canada or the United States. Other combined therapy with estrogen and progestin may also increase the risk of breast cancer, so the risks and benefits must be considered.[9]

Obesity and Height

Ovarian cancer risk increases with increasing height and weight (body mass index [BMI]).[10] The Collaborative Group on Epidemiological Studies of Ovarian Cancer compiled individual data, both published and unpublished, from 47 epidemiological studies including 12,157 women with ovarian cancer and 81,311 controls. RR increased significantly with increasing height (1.07 per 5 cm of height) and with increasing BMI (1.10 per 5 kg/m^2). These findings were

unaffected by other factors known to be associated with ovarian cancer risk, with the exception that ever-users of hormone therapy had no increased risk with increasing BMI. Given that height, weight, and BMI are thought to be strongly correlated, separating out the individual effects can be difficult.[11,12] Ovarian cancer mortality has also been shown to be increased in obese women.[13,14]

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Factors With Adequate Evidence of a Decreased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

Factors associated with a decreased risk of ovarian cancer include multiparity, use of oral contraceptives, breastfeeding, and risk-reducing surgical procedures like tubal ligation, salpingectomy, and salpingo-oophorectomy.[1-5] Each of these contributes to a decrease in ovulatory years. Pooled data from 25 case-control studies conducted by the Ovarian Cancer Association Consortium was used to quantify the association between lifetime ovulatory years and epithelial ovarian cancer risk. Lifetime ovulatory years was calculated by subtracting the years of anovulation from an individual's menstrual span (i.e., age at last menstrual period subtracted from age at menarche).[6] The odds ratio (OR) for ovarian cancer per lifetime ovulatory year with anovulation caused by pregnancy, oral contraceptive use, and breastfeeding was 1.041 (95% confidence interval [CI], 1.036–1.045).

Multiparity

Compared with nulliparous women, the risk of ovarian cancer was reduced by 30% to 60% among parous women, with additive protection for each additional birth.[1] The risk of developing ovarian cancer was lower for parous women (relative risk [RR], 0.69; 95% CI, 0.64–0.74) than for women who never had children, with increased risk reduction with increasing number of children for one child (RR, 0.82; 95% CI, 0.43–0.91) to four or more children (RR, 0.58; 95% CI, 0.53–0.64).[7]

Oral Contraceptives

A collaborative analysis was performed of individual data from 23,257 women with ovarian cancer and 87,303 women without ovarian cancer from 45 studies in 21 countries.[8] Oral contraceptive use was associated with a dose-response effect by duration of use, without observed changes in risk reduction by decade of use from the 1960s to 1980s, over which time the amount of estrogen in oral contraceptives was approximately halved. No risk reduction was observed for women who used oral contraceptives for less than 1 year. The risk reduction associated with use from 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 years or more was 0.78 (99% CI, 0.73–0.893), 0.64 (99% CI, 0.59–0.69), 0.56 (99% CI, 0.50–0.62), and 0.42 (99% CI, 0.36–0.49), respectively. The observed risk reduction persisted after cessation of oral contraceptive therapy but attenuated over time since last use. The proportional reduction in risk per 5 years of use was 29% (95% CI, 23%–34%) for women who had discontinued use within the last 10 years. The reduction in risk was 15% (95% CI, 9%–21%) for women who discontinued use 20 to 29 years ago.[9]

A meta-analysis, in which the primary analysis was restricted to 24 case-control and cohort studies published since 2000 to reflect more recent types of oral contraceptive preparations, also observed a dose-response by duration of use.[2] The authors estimated that 185 women needed to be treated for 5 years to prevent one case of ovarian cancer. Based on an estimated lifetime risk of 1.38% and prevalence of ever-use of oral contraceptives of 83%, the authors estimated a lifetime relative reduction of ovarian cancer attributable to oral contraceptives of 0.54%. A prospective cohort study from Denmark, which represented nearly 1.9 million women, also examined contemporary oral contraceptive formulations and found that current oral contraceptive formulation users had an RR reduction of 0.58 (95% CI, 0.49–0.68), and former oral contraceptive formulation users had a RR reduction of 0.77 (95% CI, 0.66–0.91). The benefits were strengthened by longer duration of use and weakened by more time since last use. No benefit was found for progesterone-only birth control products. This study was limited by only including incident ovarian cancers that occurred in women younger than 50 years.[10]

For specific information related to ovarian cancer risk among *BRCA1/BRCA2* mutation carriers, see Genetics of Breast and Gynecologic Cancers.

Depot-Medroxyprogesterone Acetate

Limited information is available on the use of injectable progestational contraceptives (depot-medroxyprogesterone acetate [DMPA]) and the risk of ovarian cancer. Studies are confounded by the use of other contraceptive methods, particularly oral contraceptives. A hospital-based study conducted in Mexico and Thailand, with 224 cases and 1,781 controls (the World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives), did not observe an association between DMPA and ovarian cancer (RR, 1.07; 95% CI, 0.6–1.8).[11] However, only 22 of the participants had ever used DMPA, and nine of them had used it for 6 months or less.

A subsequent multicenter study conducted in 12 hospitals in Thailand, including 330 cases and 982 matched controls, observed a statistically significant decreased risk of ovarian cancer associated with DMPA use, controlling for oral contraceptive use and other associated factors (OR, 0.52; 95% CI, 0.33–0.88). A dose-response association was observed, but the sample size was limited in longer-term use categories.[12]

Tubal Ligation

A meta-analysis of 16 case-control studies, three retrospective studies, and two prospective cohort studies observed a decreased risk of ovarian cancer associated with tubal ligation (RR, 0.66; 95% CI, 0.60–0.73).[4] The reduced risk was observed up to 14 years after tubal ligation. A population-based case-control study of 902 cases and 1,802 controls published subsequent to the meta-analysis observed an adjusted OR of 0.62 (95% CI, 0.51–0.75) associated with a history of a tubal ligation.[13] The association was adjusted for oral contraceptive use, which was also associated with a lower risk of ovarian cancer (OR, 0.62; 95% CI, 0.47–0.85) and other risk factors.[13] Salpingectomy has also been discussed as a preferred means of sterilization.[14,15] For more information, see the Salpingectomy section.

Another pooling project with primary data from 13 population-based case-control studies examined the association between tubal ligation and ovarian cancer risk. It included 7,942 individuals with epithelial ovarian cancers and 13,904 controls.[16] Overall, tubal ligation was associated with a 29% reduction in risk (OR, 0.71; 95% CI, 0.66–0.77). The observed risk reduction varied by subtype of invasive cancers and was 52% (OR, 0.48; 95% CI, 0.40–49) for endometrioid cancer; 48% (OR, 0.52; 95% CI, 0.40–0.67) for clear cell cancer; 32% (OR, 0.68; 95% CI, 0.52–89) for mucinous cancer; and 19% (OR, 0.81; 95% CI, 0.74–0,89) for serous cancer.

A pooled analysis from 21 prospective cohort studies examined 14 hormonal, reproductive, and lifestyle factors by histological subtype among 5,584 women with invasive ovarian cancer within a total sample of 1.3 million participants. Overall, tubal ligation was associated with an 18% reduction in risk (OR, 0.82; 95% CI, 0.73–0.93). The observed risk reduction varied by subtype of invasive cancer and was 40% (OR, 0.60; 95% CI, 0.41–88) for endometrioid cancer; 65% (OR, 0.35; 95% CI, 0.18–0.69) for clear cell cancer; and 9% (OR, 0.91; 95% CI, 0.79–1.06) for serous cancer. There was a nonsignificant increase in risk of 1% (OR, 1.01; 95% CI, 0.60–1.71) for mucinous cancer.[7]

Breastfeeding

A meta-analysis [3] that included five prospective studies and 30 case-control studies examined the association between breastfeeding and the risk of ovarian cancer. Any breastfeeding was associated with a decreased risk of ovarian cancer (RR, 0.76; 95% CI, 0.69–0.83). The risk of ovarian cancer decreased 8% for every 5-month increase in duration of breastfeeding (95% CI, 0.90–0.95). Another meta-analysis that included five prospective studies and 35 case-control

studies found that any breastfeeding was associated with a decreased risk of ovarian cancer (RR, 0.70; 95% CI, 0.64–0.76). These results are consistent with a previous meta-analysis and further support the prior finding of a suggested association between increased duration of breastfeeding and greater levels of protection.[17] Another meta-analysis of 19 studies, including four cohort and 15 case-control studies, found an overall decreased risk of ovarian cancer with an OR of 0.66 (95% CI, 0.57–0.76) and an association with duration (2% decrease per month). The benefit of breastfeeding was greatest for the first 8 to 10 months.[18]

Risk-Reducing Salpingo-Oophorectomy

Risk-reducing surgery is an option considered by women who are at high risk of ovarian cancer, such as those with an inherited susceptibility to cancer. For more information on this as a risk-reducing intervention, see the Oral contraceptives section in Genetics of Breast and Gynecologic Cancers. Among women in the general population, opportunistic salpingectomy, oophorectomy, or salpingo-oophorectomy have been considered as possible interventions at the time of surgery for other benign indications.

Harms

Risks associated with benign oophorectomy (with or without salpingectomy or hysterectomy) have been analyzed in six published studies. Studies of three cohorts found that oophorectomy performed before menopause (age 45 or 50 years) was associated with increased overall mortality, likely related to cardiovascular disease. This finding was noted particularly among individuals not using hormone replacement. In the Women's Health Initiative, bilateral salpingo-oophorectomy was not associated with increased mortality. In the National Health and Nutrition Examination Survey (NHANES III), oophorectomy overall was not related to mortality, but mortality was increased among obese women younger than 40 years who did not use hormone replacement. The California Teachers Study did not find a mortality risk with oophorectomy, but only 3% of women did not use hormone replacement. Overall, data suggest that oophorectomy among younger women likely increases overall mortality and that this risk may be attenuated with hormone replacement.[19-24] Risk-reducing salpingo-oophorectomy has been associated with worsened menopausal symptoms, decreased sexual activity, and decreased sexual functioning.[25]

Salpingectomy

Data relating salpingectomy to risk of ovarian/tubal cancer are limited but consistent. A meta-analysis of three studies found an OR of 0.51 (95% CI, 0.35–0.71) for risk of these cancers among women who had undergone salpingectomy, compared with women who had intact fallopian tubes.[5] These studies included a Swedish record linkage study conducted from 1973 to 2009 with a mean follow-up of 23 years, which found the following hazard ratios (HRs) for risk of ovarian cancer, compared with women who had not undergone surgery:

- For hysterectomy, the HR was 0.79 (95% CI, 0.70–0.88).
- For hysterectomy with bilateral salpingo-oophorectomy, the HR was 0.06 (95% CI, 0.03–0.12).
- For salpingectomy, the HR was 0.65 (95% CI, 0.52–0.81).
- For sterilization procedures, the HR was 0.72 (95% CI, 0.64–0.81).

Another population-based cohort study of all individuals in British Columbia, Canada, between 2008 and 2017, examined observed versus expected rates of ovarian cancer among individuals who had undergone opportunistic salpingectomy. The study included 25,889 individuals who underwent opportunistic salpingectomy, compared with 32,080 individuals who underwent hysterectomy alone or tubal ligation. There were no serous ovarian cancers in the opportunistic-salpingectomy group, which had a significantly lower rate than the age-adjusted expected rate of 5.27 (95% CI, 1.78–19.29) serous cancers.[26] Furthermore, another study showed that the protection of bilateral salpingectomy was approximately twice that of unilateral salpingectomy.[27] This report included limited covariate data, but results were similar to other smaller studies included in the meta-analysis. Limited data based on circulating surrogate markers of ovarian reserve suggest that salpingectomy does not have an adverse effect on ovarian function.[28,29]

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Factors With Inadequate Evidence of an Association Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

Dietary Factors

No consistent association has been observed between a variety of dietary factors and the risk of ovarian cancer.

A systematic review and meta-analysis that included 23 case-control studies and three cohort studies found no evidence of an association between alcohol use and epithelial ovarian cancer.[1]

A case-control study of the Healthy Eating Index (HEI), based on current U.S. Department of Agriculture dietary guidelines, found no association between the highest HEI score and ovarian cancer risk for any specific food group.[2] A systematic review of the role of diet in ovarian cancer included only prospective studies, with at least 200 reported cases in the publications.[3] Twenty-four publications from ten cohort studies were reviewed, and no dietary factors were consistently associated with the risk of ovarian cancer.

Aspirin and Nonsteroidal Anti-Inflammatory Drugs

A systematic review and meta-analysis of 21 observational studies found a decreased risk of invasive ovarian cancer associated with aspirin use (relative risk [RR], 0.88; 95% confidence interval [CI], 0.79–0.98), but no statistically significant association with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).[4] A study published after that review examined NSAID use and ovarian cancer risk in the National Institutes of Health–AARP Diet and Health Study. No association was observed between the development of ovarian cancer and regular aspirin use (RR, 1.06; 95% CI, 0.87–1.29) or NSAID use (RR, 0.93; 95% CI, 0.74–1.15).[5] A population-based case-control study [6] of 902 incident cases and 1,802 population controls observed a decreased risk of ovarian cancer associated with continual use (0.71; 95% CI, 0.53–0.97) or low-dose daily use (0.72; 95% CI, 0.53–0.97). In that study, selective cyclooxygenase-2 NSAIDs, but not nonselective NSAIDs, were associated with a decreased risk of ovarian cancer (odds ratio [OR], 0.60; 95% CI, 0.39–0.94). A cohort analysis of about 200,000 women in the Nurses' Health Studies, which used detailed data about the intensity and duration of aspirin use over time, showed a reduced hazard ratio (HR) for ovarian cancer of 0.77 (95% CI, 0.61–0.96) for low-dose aspirin use (≤100 mg/d) but no reduction for standard-dose aspirin use (HR, 1.17; 95% CI, 0.92–1.49).[7]

Perineal Talc Exposure

Results from case-control and cohort studies are inconsistent, so the data are inadequate to support an association between perineal talc exposure and an increased risk of ovarian cancer.

A meta-analysis of 16 studies observed an increased risk with the use of talc (RR, 1.33; 95% CI, 1.16–1.45); however, a dose-response relationship was not found.[8] A pooled analysis from the Ovarian Cancer Association Consortium, composed of multiple case-control studies, included 8,525 cases and 9,859 controls. The analysis found a modest increased risk of

epithelial ovarian cancer associated with genital powder use (OR, 1.24; 95% CI, 1.15–1.33), but the trend across increasing lifetime number of applications was not statistically significant (*P* trend = .17).[9] A meta-analysis of ten case-control studies and a highly selected subset analysis of one prospective cohort study found an association (OR, 1.47; 95% CI, 1.31–1.65) among women who used perineal talc at least twice a week.[10] The subset analysis of the prospective study was inconsistent with the main findings of the original report.[11] However, because of the structure of this analysis, the results should be interpreted with care.[10] A population-based case-control study of African American women in the United States found an association between genital powder use and risk of epithelial ovarian cancer (OR, 1.44; 95% CI, 1.11–1.86).[12] In this study of 584 cases and 745 controls, a dose-response relationship for *any* genital powder use was reported. Specifically, among *any* genital powder use, daily powder use was associated with increased adjusted OR of developing ovarian cancer (OR, 1.71; 95% CI, 1.26–2.33) compared with less than daily use (OR, 1.12; 95% CI, 0.80–1.58).

A cohort study among nurses did not observe a risk of ovarian cancer associated with perineal talc use (RR, 1.09; 95% CI, 0.86–1.37), and there was no evidence of increasing risk with increasing frequency of use.[13] Another prospective study, the Women's Health Initiative, examined the association between perineal powder use and the development of ovarian cancer among 61,576 women without a history of cancer at enrollment and who provided exposure information. Among this group, 429 cases of ovarian cancer occurred. Powder use on genitals, sanitary napkins, and diaphragms was examined individually and as a combined exposure. Women were followed for a mean of 12.4 years. An association of ovarian cancer with ever-use was not found when analyzed either by individual method of exposure or by overall combined exposure. The observed risk (HR) for combined exposure to perineal powder was 1.06 (95% CI, 0.87–1.28), and there was no increased risk observed for increasing duration of use.[14] The cohort study cited above,[11] which included 250,000 women enrolled in four long-term studies of women's health, was consistent with other cited cohort studies, as the risk of ovarian cancer in perineal talc exposure never-users was similar to that in ever-users, with an HR of 1.08 (95 % CI, 0.99–1.17).[11]

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Areas of Uncertainty

Ovarian Hyperstimulation Due to Infertility Treatment

Controversy persists concerning the association between ovarian hyperstimulation and ovarian cancer. Results of a systematic review and meta-analysis of nine cohort studies comprised 109,969 women who were exposed to ovarian hyperstimulation for infertility treatment (i.e., *in vitro* fertilization [IVF]), with 76 incident ovarian cancer cases observed, provided inconclusive evidence for an association.[1] An increased risk of ovarian cancer was observed when the comparison group was the general population (relative risk [RR], 1.50; 95% confidence interval [CI], 1.17–1.92), but no statistically significant increased risk was observed when the reference group was unexposed infertile women (RR, 1.26; 95% CI, 0.62–2.55). A major limitation was that only one of the cohort studies included in the meta-analysis had a follow-up period longer than 10 years for those exposed to IVF.

A Cochrane systematic review that included 11 case-control studies and 14 cohort studies, for a total of 186,972 women, was also indeterminate for an association. Summary statistics were not calculated because of methodological and clinical heterogeneity. Among seven cohort studies that compared treated women with untreated subfertile women, no excess risk was noted in association with hyperstimulation medications. Two cohorts noted an increased risk of twofold to fivefold when treated women were compared with the general population. An increased risk of borderline ovarian tumors was noted in three case-control studies and two cohort studies. Overall, the authors concluded there was no convincing evidence that an increased risk of invasive ovarian tumors was associated with fertility drug treatments.[2]

After the Cochrane review, a follow-up study of an infertility cohort [3] was published. A retrospective cohort of 9,825 women enrolled between 1965 and 1988 was followed through 2010. Ovarian cancer occurred in 85 women. Overall, there was no association between ovarian cancer and clomiphene citrate (RR, 1.34; 95% CI, 0.86–2.07) or gonadotropins (RR, 1.00; 95% CI, 0.48–2.08). Among the subgroup of women who remained nulligravid after treatment, an increased risk of ovarian cancer was associated with clomiphene citrate (RR, 3.63; 95% CI, 1.36–9.72). No increased risk was observed among women who successfully conceived after being treated, compared with women who were not treated.

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Latest Updates to This Summary (03/06/2024)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Incidence and Mortality

Updated statistics with estimated new cases and deaths for 2024 (cited American Cancer Society as reference 1).

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About This PDQ Summary

Purpose of This Summary

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